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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,389	06/04/2001	Hermann Bujard	BBI-009C3CN2	5305

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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/874,389	BUJARD ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 5, 2005 has been entered.

Claims 21-54 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-35, 37-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a transgenic mouse comprising a transgene comprising a nucleic acid sequence encoding luciferase operably linked to a tetracycline-responsive promoter ($p_{hCMV^{*}-1}$ (SEQ ID NO.8)) integrated into the genome of the mouse and a nucleic acid sequence encoding the reverse Tc-controlled transactivator including a nuclear localization signal (tTA^{R} (SEQ ID NO. 1)) integrated into the genome of the mouse

does not reasonably provide enablement for

the full breadth of any transgenic non-human animal comprising a transgene integrated into the genome of the animal and a tet-operator-linked gene in the genome of the animal wherein:

1) the transgene comprises a transcriptional regulatory element functional in cells of the mouse operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a mutated Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which activates transcription in eukaryotic cells,

said transgene is expressed in cells of the mouse at a level sufficient to produce amounts of said fusion protein that are sufficient to activate transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the mouse, said fusion protein binds to the tet operator-linked gene and activates transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable levels, wherein the level of expression of the tet operator-linked gene can be down modulated by depleting tetracycline or a tetracycline analogue from the mouse;

2) the transgene comprises a transcriptional regulatory element functional in cells of the mouse operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a mutated Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells,

said transgene is expressed in cells of the mouse at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the mouse, said fusion protein binds to the tet operator-linked gene and inhibits transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable levels, wherein the level of expression of the tet operator-linked gene can be up regulated by depleting tetracycline or a tetracycline analogue from the mouse; or

3) the transgene comprises a transcriptional regulatory element functional in cells of the mouse operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription of said tet operator linked gene,

the fusion protein comprises a first polypeptide which is a Tet repressor that binds to a tet operator sequence in the presence of tetracycline or a tetracycline analogue operatively linked to a second polypeptide which inhibits transcription in eukaryotic cells,

said transgene is expressed in cells of the mouse at a level sufficient to produce amounts of said fusion protein that are sufficient to inhibit transcription of the tet operator linked gene

in the presence of tetracycline or a tetracycline analogue in the mouse, said fusion protein binds to the tet operator-linked gene and inhibitss transcription of the tet operator linked gene such that the tet operator-linked gene is expressed at detectable levels, wherein the level of expression of the tet operator-linked gene can be upregulated by depleting tetracycline or a tetracycline analogue from the mouse,

for reasons of record set forth in the Office Actions of January 16, 2004, October 15, 2004, and as discussed below. It is noted that compared with the Office Actions of January 16, 2004 and October 15, 2004, the present scope of enablement is narrower. The scope of the previous Office Actions was transgenic mice. However, now, the scope has been narrowed to the mice taught in the specification. The scope is narrower because in light of the teachings of Hammer et al., as discussed in the previous Office Actions, an artisan cannot predict what the phenotype is of a transgenic mouse comprising the tet system, wherein any heterologous protein is expressed. Because the art teaches unpredictability in phenotype exhibited by transgenic mice that overexpress heterologous proteins and the specification does not teach an artisan how to overcome the teachings of the art, an artisan would need to determine empirically whether each heterologous protein expressed in a transgenic mouse has a phenotype corresponding to the overexpression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the Office Actions of January 16, 2004 and October 15, 2004. Claim 36 is rejected for a full lack of enablement as claim 36 does not comprise any enabled elements.

Response to Arguments

Applicant's arguments filed April 5, 2004 have been fully considered but they are not persuasive.

The Applicant argues that a) the specification provides sufficient guidance to allow a skilled artisan to make the claimed "non-human transgenic animal" without undue experimentation (Applicant's response, page 10), b) the state of the art at the time of invention shows that transgenic animals were produced using established methods without undue experimentation (Applicant's response, page 11), and c) the claims are enabled because the specification provides extensive guidance of how to make the claimed invention for the broad scope of any transgenic animal comprising the tet system (Applicant's response page 12).

The Applicant provides the argument that there is sufficient guidance to allow a skilled artisan to make the claimed "non-human transgenic animal" without undue experimentation. The Applicant points out that the specification provides detailed

working examples illustrating how to make the claimed invention. The Applicant points to examples that include how to select a Tet repressor, a tet inducible transcriptional activator, and how to use the claimed components to regulate expression (Applicant's response, page 10, 2nd parag. under point a). The Applicant also points to the fact that making transgenic animals by microinjection is well known in the art (Applicant's response, page 11, 1st parag. and page 11, point b) and the specification teaches that a transgenic animal of the claimed invention is made via microinjection (Applicant's response, page 11, 1st parag.).

With regards to the Applicant's arguments to the Enablement issues, while the Applicant addresses issues regarding making transgene nucleic acid constructs and injecting the constructs into fertilized oocytes obtaining animals comprising the transgene nucleic acid construct, this is not the issue that is being raised by the Examiner. Rather, the issue at hand is: how does an artisan predictably identify any non-human transgenic animal comprising the tet system such that an artisan can use the transgenic non-human animal.

First, as pointed out in the Office Action of January 16, 2004, page 3, 4th parag. to page 5, 1st parag., with regards to Cameron 1997, Molecular Biotechnology, 7: 253-265, Cameron teaches that one problem with transgenesis is integration of the transgene into the genome. There is unpredictability with regards as to where the transgene integrates in the genome and how many copies of the transgene integrate into the genome. Subsequently, the problems that arise from these random issues is that an artisan cannot predict how strongly the transgene expresses and in what tissues

the transgene expresses. Depending upon the expression pattern presented in the transgenic non-human animal, an artisan would need to decide whether the transgenic non-human animal is useful for the studies in which it will be used. The issue of generating the transgenic non-human animal, the characterization of the transgene expression profile (e.g. tissue specific and developmental period specific), and determining whether the transgenic animal has application in a study is empirically determined. To characterize and predict each and every transgenic non-human animal that can be generated and used is undue experimentation. The claims, as filed, also encompass non-human animals comprising transgene expression, wherein the phenotype is unpredictable. Nothing in the specification or the art teaches how to use any non-human transgenic animal comprising no phenotype. Nothing in the specification or art teaches how to use a non-human transgenic animal, wherein the phenotype is lethality. As such, the claimed invention is limited to what was taught in the specification: a transgenic mouse comprising a transgene comprising a nucleic acid sequence encoding luciferase operably linked to a tetracycline-responsive promoter (p_{hCMV^*-1} (SEQ ID NO.8)) integrated into the genome of the mouse and a nucleic acid sequence encoding the reverse Tc-controlled transactivator including a nuclear localization signal (tTA^R (SEQ ID NO. 1)) integrated into the genome of the mouse.

Second, as pointed out in the Office Action of January 16, 2004, page 4, 2nd parag., Hammer et al. (1990, Cell, 63: 1099-1112), teach that integration of a transgene into an alternative species of animal may result in widely different phenotypic responses. Hammer et al. teach in their example that rats and mice, which are both

rodents, had different phenotypic responses to the same construct. Hammer et al.'s teaching indicates that an artisan cannot predict that any heterologous protein will have a predictable effect on every transgenic non-human animal that express it. With regards to the instant invention, in light of the teachings of Hammer et al., the claimed invention encompasses transgenic non-human animals that express a heterologous protein, but have no phenotype, or have an unexpected phenotype. With respect to transgenic non-human animals that express a heterologous protein but have an unexpected phenotype, nothing in the art or the specification teaches an artisan how to use transgenic non-human animals comprising an unexpected phenotype. For an artisan to enabled for the full breadth of the instant invention, an artisan would need to predict all unexpected phenotypes in all non-human transgenic animals comprising a heterologous gene of interest. This is undue experimentation as nothing in the art or the specification teaches an artisan how to overcome the unpredictability of unexpected phenotypes. Alternatively, in order for an artisan to be enabled for the full breadth of the instant invention, an artisan would need to generate transgenic non-human animals from all species of non-human animals comprising all heterologous genes of interest. Based on the teachings of Hammer et al., wherein transgenic mice and rats comprising the same transgene have different phenotypes, and thus demonstrate that even animals belonging to the same family, rodents, cannot necessarily enable an artisan to predict that heterologous proteins have activity in transgenic animals of the same family, an artisan cannot predict from a representative few mammals, few fish, few insects, few amphibians that a heterologous protein would have predictable activity for all species of

non-human animals. Thus, the claims as filed, broadly encompass any transgenic non-human animal comprising any transgene construct comprising a nucleic acid sequence encoding any heterologous protein of interest. However, for the reasons given above, the claims are not enabling for its fullest scope.

Therefore, the teachings of Cameron and Hammer et al. indicate at the time of filing that an artisan cannot predict that any transgenic non-human transgenic animal comprising a transgene comprising a nucleic acid sequence encoding a heterologous protein of interest will have a phenotype or will have an expected phenotype. While the specification teaches one example, the specification does not teach how to overcome the teachings in the art that any transgenic non-human animal will exhibit any predictable phenotype when expressing a heterologous protein. The teachings also indicate at the time of filing that an artisan cannot necessarily predict if, when, and where a transgene construct will be expressed in a transgenic animal. Because of that unpredictability, an artisan has to characterize each transgenic non-human animal and determine if it can be used in experimental studies. The claims as filed, broadly encompass transgenic non-human animals which have unexpected or no phenotype, of which, no guidance has been provided as to how to use these animals.

Thus, for the reasons described above, while the specification enables an artisan to make and use a transgenic mouse comprising a transgene comprising a nucleic acid sequence encoding luciferase operably linked to a tetracycline-responsive promoter (p_{hCMV^*-1} (SEQ ID NO.8)) integrated into the genome of the mouse and a nucleic acid sequence encoding the reverse Tc-controlled transactivator including a nuclear

localization signal (tTA^R (SEQ ID NO. 1)) integrated into the genome of the mouse, the specification does not reasonably provide enablement commensurate with the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 24-27, 29-32 are rejected under 35 U.S.C. 112, second paragraph, for reasons of record set forth in the Office Actions of October 15, 2004 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Response to Arguments

Applicant's arguments filed April 5, 2004 have been fully considered but they are not persuasive.

Claims 21, 24-27, 29-32 are vague and indefinite because they recite the term "detectable levels." It is noted that "detectable level" is a relative word and the metes and bounds of the term cannot be determined and therefor is not clear.

While the Applicant provides the argument that an artisan would understand that "detectable levels" depends on the particular application and that an artisan would understand the limits of the different methods which was used to detect the gene of interest, the Examiner does not find the argument persuasive.

The problem with using the term "detectable levels" as written in the claims is that there is no guidance given to an artisan what "detectable levels" are relative to what particular application. Two artisans can be examining the same tissue for mRNA expression and while one artisan uses in situ hybridization, a not-very-sensitive assay, to look for mRNA expression and another artisan uses RT-PCR, a very sensitive assay, the artisan using in situ hybridization may say that there is no detectable level of mRNA, while the artisan using RT-PCR would say that there are detectable levels of mRNA. In both cases, the artisans would be correct that there is tissue that has detectable levels of mRNA and that there is tissue that there is undetectable levels of mRNA. One would be able to resolve the discrepancy if one qualified what method was used to detect the mRNA. However, nothing in the claims, provides guidance as to what conditions and parameters one would need to use to determine if an mRNA level is detectable or not.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21, 24-27, 29-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 5,912,411 for reasons of record set for in the previous Office Actions of January 16, 2004 and October 5, 2004. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the instant application are drawn to a transgenic non-human animal, which is broader in scope compared to the transgenic moue of the cited patent.

It is noted that in the event of the amendment of the pending claims to a transgenic mouse, the rejection will be changed to statutory double patenting rejection.

Claims 22, 23, 28, 37-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 5,866,755 for reasons of record set forth in the previous Office Action of January 16, 2004 and October 5, 2004. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to a transgenic non-human animal, which is broader in scope compared to the transgenic moue of the cited patent.

It is noted that in the event of the amendment of the pending claims to a transgenic mouse, the rejection will be changed to statutory double patenting rejection.

It is acknowledged from the Applicant's response, April 5, 2005, that the Applicants will address these issues upon the claims being found allowable.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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SUPERVISORY PATENT EXAMINER